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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/057,505	01/25/2002	Roger Y. Tsien	02307E-151530US	7832

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EXAMINER	
ROBINSON, HOPE A	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 12/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/057,505	TSIEN ET AL.	
	Examiner	Art Unit	
	Hope A. Robinson	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *59-61 and 79-81* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59-61 and 79-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *1/25/02* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.

2. Applicant's response to the Communication mailed September 20, 2005 on September 29, 2005 acknowledged. The Amendments filed on September 9, 2004, May 16, 2005 and June 27, 2005 have been entered in part as the claims were not entered for failing to meet the requirements under 37 CFR 1.121. The Terminal Disclaimer filed on October 31, 2005 has been received and entered.

Claim Disposition

3. Claims 1-58 and 62-78 have been canceled. Claims 79-81 have been added. Claims 59-61 and 79-81 are pending and are under examination.

Withdrawn-Specification Objections

4. Previous objection to the specification is withdrawn by virtue of submission of an amendment.

Withdrawn-Objection to Claims

5. Previous objection to claims are withdrawn by virtue of submission of an amendment, which cancelled or amended the claims.

Withdrawn-Basis For NonStatutory Double Patenting

6. Previous rejection of the claims under 35 U.S.C. 103, Obvious-type Double Patenting is withdrawn by virtue of submission of a Terminal Disclosure.

Maintained-Oath/Declaration

7. As previously stated the Oath/Declaration is objected to because non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). See for example where corrections have been made to citizenship information.

The amendment filed on June 27, 2005 state that a new Oath/Declaration is filed concurrently, however, none was found in the application (see page 8 of the response).

Correction is required.

New-Specification Objections

8. The specification is objected to because of the following informalities:

(a) The specification is objected to because the priority information needs to be updated. For example, "This application is a continuation of U.S. Application No. 09/396,003, filed September 13, 1999, now abandoned, which is a continuation of U.S. Application No.

08/792,553, filed January 31, 1997, now U.S. Patent No. 5,981,200, which is a continuation-in-part of U.S. Application No. 08/594,575, filed January 31, 1996, now U.S. Patent No. 6,803,188".

(b) The specification is objected to because Figure 1 has parts (A) and (B), however, the Brief Description of the Drawings on page 6 does not describe the figure as such.

New-Claim Objections

8. Claims 61 and 79 are objected to because of the following informalities:

(a) Claim 61 is objected to for the recitation of: (i) "interleukin-1 b-converting enzyme" instead of "interleukin-1b-converting enzyme" and (ii) "b-Secretase for APP" in lieu of "beta (or β)-secretase for amyloid precursor protein".

(b) Claim 79 is objected to because the claim recites "constrct" instead of "construct". See also a typographical error in item (ii) (b) "Ser72Ala~", instead of "Ser72Ala,".

Correction is required.

New-Claim Rejections - 35 USC ∋ 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 59-61 and 79-81 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed,

had possession of the claimed invention. The claims recite added material, which is not supported by the original disclosure. Claims 79, 80 and 81 and dependent claims hereto recite "an amino acid substantially identical to SEQ ID NO:2" and the instant specification does not provide support for this language. The instant specification disclose the following: in paragraph 0049: "As used herein, a fluorescent protein in an *Aequorea*-related fluorescent protein if any contiguous sequence of 150 amino acids of the fluorescent protein has at least 85% sequence identity with an amino acid sequence, either contiguous or non-contiguous, from the wild-type *Aequorea* green fluorescent protein of SEQ ID NO:2. More preferably, a fluorescent protein in an *Aequorea*-related fluorescent protein if any contiguous sequence of 200 amino acids of the fluorescent protein has at least 95% sequence identity with an amino acid sequence, either contiguous or non-contiguous, from the wild-type *Aequorea* green fluorescent protein of SEQ ID NO:2". Note that the specification does not disclose "by substantially identical we mean 85% or 95%" to SEQ ID NO:2". Thus, no support is found for the recited limitation in the claims. It is suggested that the claims are amended to delete the new matter. Therefore, the specification lacks adequate written description.

Maintained and Amended-Claim Rejections - 35 USC ∋ 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 79-81 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a tandem fluorescent protein construct, comprising a donor fluorescent protein moiety, an acceptor fluorescent protein moiety and a linker moiety that couples the donor and acceptor moieties and wherein the donor and acceptor moieties exhibit FRET when the donor moiety is excited by radiation, characterized in that the linker moiety comprises a protease cleavage recognition site, wherein cleavage of the linker by a protease results in a change in FRET between the donor and acceptor moieties. The claims are also directed to donor and acceptor moieties comprising an amino acid sequence 'substantially identical' to SEQ ID NO:2 and SEQ ID NO:2 comprising several amino acid substitutions that are combined. Essentially the claims encompass any structure as long as said structure comprises the above mutation. Thus, the claims encompasses other mutations not defined which could result in a structure that would not produce FRET and neither the claims nor specification sets forth what is considered to be substantial identity with SEQ ID NO:2. There is no indication that run of amino acids of 150 or 200 contiguous residues is required to meet the 'substantial identity' limitation. The claims encompass a genus of proteins not described or defined. Further, the specification fails to provide any additional representative species of the claimed genus to show that applicant was in possession of the claimed genus.

A representative number of species means that the species, which are adequately described are representative of the entire genus. The written description requirement for a

claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

12. Claim 79-81 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a donor fluorescent protein moiety and an acceptor fluorescent moiety contained in SEQ ID NO:2 with specific mutations to SEQ ID NO:2 at the positions listed in for example claim 79 and the disclosure in U.S. Patent No. 5,981,200, (for example, wherein the linker is a peptide moiety that does not emit light to excite the donor fluorescent protein moiety), does not reasonably provide enablement for mutations to the donor and acceptor moieties that are "substantially identical to SEQ ID NO:2" that may not produce FRET. In addition, the claims read on any linker and the specification is not enabled for any linker as the linker moiety may refer to a single amino acid or a group or any linker with a protease recognition site for any protease. While the specification is enabled for linkers that are not fluorescent, is not enabled for linkers that are fluorescent. Further, the specification while enabled for linkers about 5-50 amino acids (see page 2 of the specification) is not enabled for linkers with the lengths encompassed in the breath of the claims.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: quantity of experimentation necessary; amount of direction or guidance presented; presence or absence of working examples; nature of the invention; state of the prior art relative skill of those in the art; predictability or unpredictability of the art and breadth of the claims, each of which will be discussed below.

The claims are directed to a tandem fluorescent protein construct, comprising a donor fluorescent protein moiety, an acceptor fluorescent protein moiety and a linker moiety that couples the donor and acceptor moieties and wherein the donor and acceptor moieties exhibit FRET when the donor moiety is excited by radiation, characterized in that the linker moiety comprises a protease cleavage recognition site, wherein cleavage of the linker by a protease results in a change in FRET between the donor and acceptor moieties. The specification on page 8, line 12-15 appears to describe linkers as encompassing in scope those molecules that can be fluorescent in the same manner as the donor and acceptor moieties (in defining the "linker moiety" as a "radical" in the same manner as the fluorescent protein moieties). The specification only provides guidance for the use of linkers as a non-fluorescent moiety that provides at least the appropriate degree of separation between donor and acceptor moieties. There is no guidance to use the linker in any other manner, and the effect of having an additional fluorescent moiety between the donor and acceptor would have unpredictable consequences on resonance transfer,

which as taught on page 12 of the instant specification is extremely sensitive to the degree of separation between donor and acceptor. One of skill in the art would have to engage in undue experimentation to provide linkers with the properties encompassed by the claims given these factors. The claims are also directed to donor and acceptor moieties comprising SEQ ID NO:2 comprising several amino acid substitutions. Therefore the claims encompass undefined structures or multiple fluorescent moieties for which the specification is not enabled. To construct and test the many protein fragments encompassed in the claim to see the desired properties are retained would require undue experimentation.

Additionally, the specification fails to describe or provide any identifying characteristics or properties for the "other mutations" encompassed in the open claim language or provide data to demonstrate that function is retained or that the protein moieties exhibit FRET. Therefore, while it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship. For example, Heim et al. (PNAS, vol. 91, pages 12501-04, 1994) disclose that a mutated DNA was sequenced and found to contain five amino acid substitutions, only one of which was found to be critical, Tyr66His, in the center of the chromophore. Heim et al. also disclose further site directed mutagenesis and noted that there was tolerance of the substitutions made, however, some mutants were weakly fluorescent (page 12504). The substitutions contemplated by the instant invention is greater than that proposed in the art, hence the specification should provide guidance as to what portion of the sequence is conserved and define the "other mutations" encompassed in the "comprising" language.

In addition, the specification on page 20, line 31 discloses that the optimal distance between the donor and acceptor sites is between about 1nm to about 10nm for the claimed resonance energy transfer to be useful. However, the "fluorescent protein moieties" encompass fluorescent peptide fragments of the intact fluorescent proteins, the distance between donor and acceptor may be about as short as the length of the linker. On page 20 of the specification it is stated that the length of the linker moiety is chosen to optimize both FRET and the kinetics and specificity of enzymatic cleavage. Thus, if the linker is too short, the protein moieties may sterically interfere with each other's folding or with the ability of the cleavage enzyme to attack the linker. However, the claims broadly encompass linkers that are greater than 5-50 amino acids or 1-10nm in length which is not supported by the instant specification that discloses that linker length is a critical parameter required for the tandem conjugates to work and that linker lengths beyond about 1-10nm would unpredictably result in interference with polypeptide folding, enzyme cleavage, insufficient resonance transfer, or linker cleavage specificity. Moreover, the claims recite two fluorescent protein moieties said to be linked to one another via a linker moiety, the specification does not provide guidance as to covalent binding occurring via cyclization and oxidation of amino acids of the donor and acceptor protein moieties, or via any other methods considered to produce the "coupling" of the donor and acceptor protein moieties. No information is provided as to how the individual fluorescent moieties are to be isolated and ultimately linked to one another via any linking moiety. Thus, absent adequate guidance/direction regarding for example, the linker length, based on the breath of the claims, the undefined structures encompassed by the claims, the nature of the invention and the

unpredictability of the linker as recited in the claims, a skilled artisan would not be able to practice the claimed invention commensurate in scope with the claims.

In view of the foregoing, one of skill in the art would require guidance, beyond that provided in the instant specification, in order to make the claimed tandem fluorescent protein in a manner that reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

Response to Arguments

13. The response filed on June 27, 2005 has been considered, however, is not fully persuasive. Note that new grounds of rejections have been instituted under 35 U.S.C. 112, first paragraph for the reasons stated above. In addition, the rejections under 35 U.S.C. 112 first paragraph written description and enablement have been maintained.

Regarding the art rejection maintained under 35 U.S.C. 112 first paragraph written description, applicant on pages 8-9 state that 'comprising' has been deleted from the claims and state that applicant does not need to define all the members of a claimed genus nor must all the members of that genus be biologically functional. Applicant opines that the newly submitted claims, obviate this rejection. However, this assertion is not correct as the claims recite donor and acceptor sequences that are 'substantially identical' to SEQ ID NO:2 and a skilled artisan cannot envision the detailed chemical structure of said proteins absent adequate written description. What does the structure of the donor, acceptor and linker look like, in view of the substantially identical language and the little description provided in the claims. Thus, the claims encompass a large variable genus of proteins. Therefore the rejection remains.

Regarding the rejection under 35 U.S.C. 112, first paragraph enablement, applicant on page 9-10 state that the linker language presented in the instant application is the same as given in their patents which are related to this application. This argument is not germane to the enablement issues raised, furthermore, each application is treated individually. The issue at hand is the breath of the claims in view of the art and guidance provided in the specification. Page 8 of the specification defines the linker as a radical and also defines a fluorescent protein moiety as a radical, which is problematic with respect to the energy transfer desired. The other issue raised is that the claims broadly read on any sequence that possess the mutations set forth in claim 79, as the instant specification does not define what is considered to be substantially identical, for example, 50% or 85% sequence identity.

The issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record. This make and test position is inconsistent with the decisions of *In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)* where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)*. Thus, the rejection remains.

Conclusion

14. No claims are allowable.

15. Applicant's amendment necessitated the new/modified ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr, can be reached at (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hope Robinson, MS

Patent Examiner 12/19/05

KATHLEEN M. KERR, PH.D.
SUPERVISORY PATENT EXAMINER